Secondary prophylaxis in adolescent and adult haemophiliacs

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Progressive arthropathy of large joints of the limbs (knees, ankles, elbows), resulting from recurrent joint bleeds and subsequent long-term degenerative phenomena, is one of the main causes of morbidity and of deterioration of quality of life in adult severe hemophiliacs. While primary prophylaxis (i.e. the regular continuous long-term infusion of factor concentrates started before the age of two years and/or after no more than one joint bleed) is nowadays considered the gold standard for preserving joint function in patients with severe haemophilia, the benefits of secondary prophylaxis (i.e., all the long-term regular treatments not fulfilling the criteria of primary prophylaxis) are still controversial.

In this review we present the literature data on secondary prophylaxis, focusing on adolescent and adults haemophiliacs along with clinical experience in Italy.

On the whole, the more recently published studies suggest the effectiveness of early and delayed secondary prophylaxis. However, a number of questions are still unanswered, including the optimal dose, dosing interval and duration of secondary prophylaxis. Only large, prospective, long-term, possibly randomized studies will help to definitively assess the clinical impact of this strategy in adolescent and adult hemophiliacs.

Key Words: secondary prophylaxis, haemophilia, adolescent-adult, cost/effectiveness, quality of life.

Introduction

Progressive arthropathy of large joints of the limbs (knees, ankles, elbows), resulting from recurrent joint bleeds and subsequent long-term degenerative phenomena[1], is the main cause of morbidity and of deterioration of quality of life in adults with severe haemophilia. Over the last four decades, the natural history of severe haemophilia has been radically transformed thanks to the availability of clotting factor concentrates and the diffusion of prophylaxis. The clinical benefits of prophylaxis, which consists of regular infusion of factor concentrates to prevent joint bleeds and their long-term sequelae, have been shown since the publication of experience from northern European countries in which it was first implemented[2-3] and are greater when prophylaxis is started at an early age[2-5]. According to the current definitions and to the aim of preserving joint structure and function, primary prophylaxis is intended as regular continuous long-term treatment started before the patient is 2 years old and/or after no more than one joint bleed, whereas secondary prophylaxis includes all long-term regular treatments not fulfilling these criteria[6]. Given its benefits, prophylaxis is recommended as the first choice of treatment for severe haemophiliacs by the World Health Organisation (WHO) and the World Federation of Hemophilia (WFH)[7] and by many national scientific societies. Recently, the Medical and Scientific Advisory Council of the US National Hemophilia Foundation (MASAC) recommended prophylaxis as the standard of care for severe haemophiliacs of all ages[8]. However, although the use of primary prophylaxis is supported by widespread clinical practice in Haemophilia Centres and by evidence from many observational and, more recently, also from a randomised controlled study[9,10], the benefits of secondary prophylaxis have been less extensively studied[11].

This review focuses on the present knowledge on secondary prophylaxis started late in life, in particular in adolescent and adult haemophiliacs.

Delayed or late secondary prophylaxis

Various studies are available in the literature on secondary prophylaxis started in children of school age or even in adolescence[12-16]. In most cases secondary prophylaxis was initiated because of a high bleeding frequency when patients were treated on-demand or after the development of target joints. The clinical impact of a delayed start of prophylaxis is shown by the results in the oldest cohort of patients described in the classic report on 25 years of experience with prophylaxis in Sweden[2]. These patients started prophylaxis at an age between 3 and 13 years old (median, 7 years) and had higher numbers of joint bleeds and of days of work-school lost, together with higher orthopaedic and radiological scores, than patients from the younger cohorts starting prophylaxis earlier[2]. Similarly, a German experience, in which the importance of the association of long-term prophylaxis with physiotherapy and physical activity is highlighted, reported better results in patients aged 9-12 years at the start of the study than in those 13-16 years old[12]. However, on the whole these studies show that even delayed prophylaxis is able to reduce the frequency of bleeding, to improve physical functioning and quality of life of children and to delay (or in some cases revert[12, 15]) the progression of arthropathy. In this respect, the Orthopaedic Outcome Study represents a milestone[13]. In this 6-year prospective multinational study involving 477 patients with a mean age of about 12 years, prophylaxis was associated with a significantly slower progression of arthropathy, the annual variation of orthopaedic and radiological scores being about one third and half, respectively, of that in patients treated on-demand[13]. Moreover this study provided data on the reduction of direct and indirect health-related costs in patients on prophylaxis, showing significant reductions in the number of hospital admissions and school absenteeism with a consequent favourable impact on the psychosocial development of haemophilic children.

Secondary prophylaxis in adolescents - adults

Only a few publications are available on secondary prophylaxis in young-adult haemophiliacs[17-23]. These reports are all retrospective and often concern small study populations (Table I). In 25 adult patients with inherited bleeding disorders on secondary prophylaxis, Miners and colleagues[17] observed a remarkable reduction of bleeding frequency (from a median of 37 bleeds per year during on-demand treatment to a median of 13 bleeds per year during prophylaxis) but this required a three-fold increase of clotting factor consumption. In a subsequent study on 61 adults with severe haemophilia, Fischer and colleagues[20] concluded that long-term secondary prophylaxis prevented joint bleeds and slowed, but did not stop, the progression of haemophilic arthropathy. A 70% reduction of bleeding episodes, with a moderate increase of factor VIII

Table I - Retrospective studies on secondary prophylaxis in adolescent and adult haemophiliacs

Author, yr	Type of publication	Patients	Median age (range), years	Main results
Miners, 1998	Full paper	19 HA, 5 HB, 1WD	30 (4-63)	↓ median number of bleeds/year (37 → 13) but 350% ↑ factor consumption
Loverin, 2000	Abstract	4 HA	-	89% mean ↓ of joint bleeds, better joint status, lower annual factor usage
Saba, 2000	Abstract	6 HA, 1 HB	37 (29-49)	↓ joint bleeds/month (4.16 → 0.48) with ↑ of costs (10,979 $ per patient/month)
Fischer, 2005	Abstract	61 HA	26 (19-43)	↓ joint bleeds/year (9.1 → 3.6) on long-term prophylaxis slows but does not stop progression of haemophilic arthropathy
Coppola, 2005	Abstract	19 HA	29 (17-46)	71% mean ↓ total bleeds, ↑ costs (23,645 € per patient/ month), improved quality of life
Tagliaferri, 2006	Letter	17 HA, 3 HB	27 (12-74)	↓ mean joint bleeds/year (26.1 → 3.4) improved orthopedic scores and well-being, ↑ 31% factor use and costs
Tagliaferri, 2008	Full paper	76 HA, 8 HB	28 (13-76)	↓ mean joint bleeds (32.4 → 3.3) and work/school days lost (32.4 →3.0), improved orthopaedic scores and higher costs in particular in adolescents, improved quality of life

HA: haemophilia A; HB: haemophilia B; VWD: von Willebrand's disease

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consumption and costs and improvement of quality of life, was registered during secondary prophylaxis in comparison with on-demand therapy by Coppola and colleagues[21]. We have recently described 20 adolescent/adult haemophiliacs switched from on-demand treatment to secondary prophylaxis[20]. This latter therapeutic regimen reduced the number of joint bleeds (from 26.1 per year during on-demand therapy to 3.4 per year during prophylactic therapy) improving patients' orthopaedic scores and well-being. More recently, in order to assess the clinical impact of secondary prophylaxis on patients with severe haemophilia in our country, we conducted a survey among members of the Italian Association of Haemophilia Centres (AICE). This retrospective survey collected data on 84 patients severely affected by haemophilia who switched from on-demand treatment to prophylaxis in adolescence (n=30) or adulthood (n=54)[21]. The switching of the patients to secondary prophylaxis significantly reduced the mean number of total and joint bleeds (35.8 versus 4.2 and 32.4 versus 3.3; $p < 0.01$, respectively) and the days of work/school lost (34.6 versus 3.0, $p < 0.01$). Furthermore, there was a statistically significant reduction in the orthopaedic score with the change from on-demand to prophylactic treatment in the adolescent group, although not in the study population as a whole. Finally, adolescent/adult haemophiliacs received significantly more (about 39%) factor concentrate, with consequently higher costs, during secondary prophylaxis than during on-demand treatment. For a subgroup of patients, data on health-related quality of life (albeit assessed by non-validated specific instruments) were also available, showing improvements of patients' satisfaction for treatment, pain/discomfort and mobility, with concurrent reductions of haemophilia-related physical restrictions and psychological impact. On the basis of these results, we concluded that the significantly higher factor consumption and costs of secondary prophylaxis, in comparison with on-demand treatment, were well balanced by the clinical improvement and greater well-being in this cohort of patients with severe haemophilia[21].

Open issues and conclusions

While primary prophylaxis remains the gold standard for preserving joint function in patients with severe haemophilia, the literature data also support the effectiveness of early secondary prophylaxis. Furthermore, recent evidence suggests that delayed secondary prophylaxis has the potential to increase joint protection as compared to that afforded by on-demand therapy, even in adulthood.

Despite the lack of controlled studies, it is unquestionable that prophylaxis at any age reduces the number of joint bleeds and, in parallel, the patients' physical and psychological restrictions, being able to radically transform the lives of severe haemophiliacs. Thus, as shown in our experience, the improvement of well-being appears to counterbalance the higher costs of secondary prophylaxis also in adolescent and adult patients. For the same reasons, the recent MASAC recommendations seem justified[8].

Whether secondary prophylaxis may slow the progression of haemophilic arthropathy in patients with established joint damage is still debated. However these benefits are likely to be more limited than in earlier prophylaxis: to what extent (or in which subset of patients) such effects are detectable remains an open issue. In view of this and of the limited resources for haemophilia treatment, the general introduction of secondary prophylaxis in adult patients raises perplexities and the selection of candidate patients on a case-by-case basis is suggested[10,24]. The reported tendency to a reduction of concentrate requirement for prophylaxis with age and the increased consumption with progression of arthropathy in patients treated on-demand, resulting in substantially comparable concentrate use when long-term follow-ups are considered[25-26], should be also taken into account. The pharmaco-economic evaluations of the cost-benefit ratio of prophylaxis should include all health-related costs, including days of hospitalisation, visits to haemophilia centres, physiotherapy cycles, orthopaedic consultations and procedures[27]. It is conceivable that secondary prophylaxis is more cost-effective in adult patients, because of a lower impact of the increase in concentrate consumption and that benefits may be even more evident in studies with long-term follow-ups[26]. Moreover, some aspects of patients' quality of life are difficult to quantify (for example, psychosocial benefits from regular school attendance and work activities, crucial in adolescent and adult patients), even in the sophisticated cost-efficacy and cost-utility models recently developed[5].

In conclusion, a number of issues remain unresolved, including the optimal dose, dosing interval and duration of secondary prophylaxis. Only large, prospective, long-term, and possibly randomised studies will help to make a definitive assessment of the clinical impact of this strategy in adolescent and adult haemophiliacs.

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Conflicts of interest disclosure

The Authors Annarita Tagliaferri and Gianna Franca Rivolta declares that they received lecture fees by CSL Behring and occasional consultancy fees for expert opinion by Bayer Shering Pharma.

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